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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/621,326	HOFFMAN ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-35* is/are rejected.

7)☒ Claim(s) *29,31,33 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 5/28/2008, are acknowledged and entered. Claims 1, 4, 7, 8, and 10-25 have been cancelled by Applicant. Claims 28-35 are newly added. Claims 26-35 are pending and under examination.

Power of Attorney

Receipt is acknowledged of the Power of Attorney, filed 4/17/2008, appointing Royal W. Craig and Ober, Kaler, Grimes, and Shriver as attorneys.

Terminal Disclaimer

Receipt is acknowledged of the Terminal Disclaimer, filed 5/27/2008. This Terminal Disclaimer was not signed and thus was not approved. However, the Terminal Disclaimer, filed 5/28/2008, was received and approved.

Petition Regarding Priority Claim

Receipt is acknowledged of the Petition to accept an unintentionally delayed claim of priority pursuant to 37 C.F.R. 1.78(A)(3), filed 5/28/2008. However, pursuant to the petition decision rendered 9/16/2008, said petition is **DISMISSED** because Applicants failed to satisfy all of the requirements of a grantable petition under 37 C.F.R. 1.78(a)(3).

Receipt is acknowledged of the Petition to accept an unintentionally delayed claim of priority pursuant to 37 C.F.R. 1.78(A)(3), filed 11/4/2008. However, pursuant to the petition decision rendered 1/8/2009, said petition is **DISMISSED** because Applicants failed to satisfy all of the requirements of a grantable petition under 37 C.F.R. 1.78(a)(3).

In view of the above Petition Decisions, the instant application is not entitled to the benefit of the prior filed PCT/IL02/00051. The earliest effective U.S. filing date afforded the instant claims is **July 18, 2003**, the filing date of the instant application.

Accordingly, WO 02/056823 remains available prior art under 35 U.S.C. 102(a) because it is "by another" and published prior to the filing date of the present application.

Response to Arguments

Any previous rejections and/or objections to claims 1, 4, 7, 8, and 10-25 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Claim Objections

Claims 29, 31, 33, and 35 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claims 29, 31, 33, and 35 recite inherent properties of the disclosed compounds (e.g., "...wherein said disulfiram oxidizes GSH to GSSG"). The claims thus do not further limit the subject matter of the claims from which they depend.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 26, Applicants recite administering to a subject a pharmaceutically effective dosage of "an agent", which implies administration of a single, specific compound. However, claim 26 subsequently recites the limitation "...said agent comprising any one *or a combination* from the group of disulfiram, curcumin, BCNU, and BSO...". The claims are thus unclear with respect to what compound or compounds are intended to be administered. Further, it is not seen how "an agent" can "comprise" another agent. Thus, the limitation "...said agent comprising any one or a combination from the group of disulfiram, curcumin, BCNU, and BSO..." renders the claims indefinite because it is not apparent whether Applicant intends that any macromolecule containing the structure of disulfiram, curcumin, BCNU, or BSO can be administered.

Claims 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Whereas the preamble of claim 26 recites a method of treating a tumor, the active method step of the claim recites the step of "...administering to a subject....". This active method step is not linked to the preamble of the claim in such a way so as to clearly convey that "a subject" being administered the claimed compound(s) has a tumor comprising malignant cancer cells as recited in the preamble.

Claims 28-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 28, 30, and 32 recite the limitations, "..wherein said agent *includes* disulfiram", "...wherein said agent *includes* curcumin", and "...wherein said agent *includes* BCNU". These limitations render claims 28, 30, and 32 and claims dependent therefrom indefinite because it is not apparent what, if anything, is intended to be excluded from the claims. In other words, it is not clear whether the claims are limited to the agent explicitly recited in the claims.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 4, 7-8, 10-21, 24, and 26-27 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of tumors with disulfiram, BSO, carmustine (BCNU) and curcumin, does not reasonably provide enablement for the treatment of tumors with the broad genera of agents contemplated by the instant claims, is **withdrawn** in light of Applicant's cancellation of claims 1, 4, 7-8, 10-21, and 24 and amendments to claims 26-27.

Claim Rejections - 35 USC § 102 – New Grounds of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26 and 34-35 are rejected under 35 U.S.C. 102(a) as being anticipated by **Hoffman** (WO 02/056823).

Hoffman teaches a method of treating malignancies through control of the redox state or environment of the cell, comprising administering a GSH-decreasing agent (Abstract). Treatment of tumors is taught at page 7, lines 25-32.

The treatment of tumors having an operative RB protein as recited in claim 26 is taught at page 7, lines 22-24.

GSH depleting agents include oxidizers of GSH (*e.g.*, α-lipoic acid, hydrogen peroxide, ascorbic acid, quinones), agents that form adducts with GSH (*e.g.,* Michael acceptors), and inhibitors of GSH (*e.g.*, BSO) (pages 9-10). Because claim 26 only requires administration of one agent selected from disulfiram, curcumin, BCNU, and BSO (*i.e.*, "...comprising any one or a combination..."), Hoffman anticipates the limitations of claim 26.

Hoffman further teaches combinations comprising more than one GSH-depleting agent as recited in the instant claims (page 13, line 10 to page 14, line 6; page 16, line 5 to page 17, line 18; page 19, lines 11-33).

Accordingly, for the above reasons, the claims are deemed properly rejected.

Claims 26 and 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by **Marikovsky** (USP No. 6,288,110; Issued Sep. 11, 2001).

Marikovsky teaches administration of disulfiram to treat angiogenesis-dependent disorders such as neoplasms (Abstract). Examples of solid tumors that can be treated with disulfiram include bladder, breast, cervix, ear, esophogus, kidney, larynx, liver, lung, ovary,

pancreas, prostate, skin, stomach, thyroid, urethra, and uterus carcinomas (col. 3, lines 1-5). These tumors anticipate the claimed tumors comprising malignant cancer cells having an operative retinoblastoma protein because, in the absence of evidence to the contrary, all cells, both normal and malignant, in the human body comprise an operative RB protein.

Marikovsky teaches administration of disulfiram of 1 mL of an aqueous solution comprising 0.1-0.5 mM disulfiram (25-120 mg) to mice bearing C6 glioma tumors (col. 6, lines 54-63; Table 1). Marikovsky further teaches that disulfiram induces apoptosis of endothelial cells (Figure 4).

Accordingly, Marikovsky anticipates the claimed method of treating tumors comprising an operative retinoblastoma protein comprising administering a pharmaceutically effective dosage of disulfiram to a subject.

Claims 26 and 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by **Sharma *et al.*** (Clinical Cancer Research, July 2001, vol. 7, pages 1894-1900).

Sharma *et al.* teach administration of *Curcuma* spp. extracts containing from 36-180 mg of curcumin to patients with advanced colorectal cancer (Abstract). The curcumin-containing tablets were administered "daily" (id.). These doses and administration schedules anticipate the claimed "pharmaceutically effective dosage" and "...consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours..." as recited in claim 26.

Advanced colorectal cancer anticipates the claimed tumors comprising malignant cancer cells having an operative retinoblastoma protein because, in the absence of evidence to the contrary, all cells, both normal and malignant, in the human body comprise an operative RB protein.

Accordingly, Sharma *et al.* anticipate the claimed method of treating tumors comprising an operative retinoblastoma protein comprising administering a pharmaceutically effective dosage of curcumin to a subject.

Claims 26 and 32-33 are rejected under 35 U.S.C. 102(b) as being anticipated by **Johnson *et al.*** (Neurosurgery, 1987, vol. 20, no. 4, pages 577-583) (Abstract attached).

Johnson *et al.* teach intracarotid administration of BCNU at a dose of 150 mg/m^2 dissolved in 5% dextrose in water to patients with documented progression of malignant glioma (Abstract). This dose and administration anticipate the claimed "pharmaceutically effective dosage" and "...consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours..." as recited in claim 26.

Malignant glioma anticipates the claimed tumors comprising malignant cancer cells having an operative retinoblastoma protein because, in the absence of evidence to the contrary, all cells, both normal and malignant, in the human body comprise an operative RB protein.

Accordingly, Johnson *et al.* anticipate the claimed method of treating tumors comprising an operative retinoblastoma protein comprising administering a pharmaceutically effective dosage of BCNU to a subject.

Claims 26 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by **Bailey *et al.*** (J. Natl. Cancer Inst., 1997, vol. 89, no. 23, pages 1789-1796).

Bailey *et al.* teach administration of an initial 30-minute infusion followed by immediate continuous infusion of BSO on one of the following schedules: 1) 0.75 g/m^2 per hour for 24 hours (4 patients); 2) 0.75 g/m^2 for 48 hours (4 patients); 3) 0.75 g/m^2 for 72 hours (10 patients); or 4) 1.5 g/m^2 per hour for 48 hours (3 patients) to patients with advanced cancers (Abstract). These doses and administration schedules anticipate the claimed "pharmaceutically effective dosage" and "...consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours..." as recited in claim 26.

Primary tumors in the treated subjects included ovarian, breast, melanoma, lung, and colon (Table 1). Such tumors thus anticipate the claimed tumors comprising malignant cancer cells having an operative retinoblastoma protein because, in the absence of evidence to the contrary, all cells in the human body comprise an operative RB protein.

The treatment resulted in consistent, profound glutathione depletion in tumor cells compared to peripheral leukocytes (Abstract; Figure 1).

Accordingly, Bailey *et al.* anticipate the claimed method of treating tumors comprising an operative retinoblastoma protein comprising administering a pharmaceutically effective dosage of BSO to a subject.

Claim Rejections - 35 USC § 103 – New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-29 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Cen *et al.*** (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204).

Cen *et al.* teach that redox regulation in melanoma cells is aberrant and that disulfiram induces apoptosis of metastatic melanoma cells at a dose of 25-50 ng/mL (Abstract; Fig. 1; Fig. 2). BSO, an inhibitor of g-glutamyl-cysteine synthetase, as a single agent also increased apoptosis and slightly enhanced the level of apoptosis induced by disulfiram when co-administered for 3 or 4 days (Abstract; Table 1). The authors teach that BSO depletes intracellular glutathione and disulfiram reduces the ratio of reduced and oxidized glutathione (Abstract; Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered disulfiram and BSO to a subject having melanoma. The skilled artisan would have been motivated to do so because each of these agents alone has been demonstrated to induce apoptosis of melanoma cells and in combination, increased apoptosis over either agent alone is observed. Disulfiram and BSO are taught in the prior art to

deplete intracellular glutathione (BSO) and reduce the $[GSH]^2/[GSSG]$ ratio (disulfiram) as recited in the instant claims.

In the absence of evidence to the contrary, the melanoma cells treated in Cen *et al.*, and in fact melanoma cells in a subject, have an "operative retinoblastoma protein" as recited in the instant claims. For example, Applicants teach that human RB protein is expressed in "every tissue type examined" (page 2, lines 28-29), plays a major role in a regulatory circuit in late G_1 (growth) phase (*id.* at lines 29-30), and is involved in regulating an elusive switch point between cell cycle, differentiation, and apoptosis (page 3, lines 3-4). As such, all cells in a subject would be expected to have an operative retinoblastoma protein. The effect recited in the instant claims (*i.e.*, dephosphorylizing the RB protein and maintaining a dephosphorylated state of the RB to induce apoptosis) would be a natural result of contacting melanoma cells in a subject with disulfiram and BSO as suggested and motivated by the prior art. Applicant's recognition of the mechanism through which disulfiram and BSO induce apoptosis of melanoma cells is not a patentable distinction over the treatment method taught in the cited prior art.

Claims 26-27 and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020).

Ali-Osman *et al.* disclose that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as recited in claims 26, 27, and 32-35. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme (see instant claim 33). Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). The reference further suggests 24-hour exposure to BSO to decrease glutathione content in glioma cells (Abstract; Fig. 5). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors, especially in view of the teachings therein where in vitro and in vivo studies and clinical trials in humans have shown

GSH depletion with BSO to be a potentially useful strategy with which to biochemically enhance the efficacy of cancer chemotherapy (page 1016, right column, "Discussion").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered BSO and BCNU to a subject having a glioma. The skilled artisan would have been motivated to do so because treatment with BSO has been shown in increase the cytotoxicity of glioma cells to BCNU.

In the absence of evidence to the contrary, the glioma cells treated in Ali-Osman *et al.*, and in fact glioma cells in a subject, have an "operative retinoblastoma protein" as recited in the instant claims. For example, Applicants teach that human RB protein is expressed in "every tissue type examined" (page 2, lines 28-29), plays a major role in a regulatory circuit in late G_1 (growth) phase (*id.* at lines 29-30), and is involved in regulating an elusive switch point between cell cycle, differentiation, and apoptosis (page 3, lines 3-4). As such, all cells in a subject would be expected to have an operative retinoblastoma protein. The effect recited in the instant claims (*i.e.*, dephosphorylizing the RB protein and maintaining a dephosphorylated state of the RB to induce apoptosis) would be a natural result of contacting glioma cells in a subject with BSO and BCNU as suggested and motivated by the prior art. Applicant's recognition of the mechanism through which BSO and BCNU induce apoptosis of glioma cells is not a patentable distinction over the treatment method taught in the cited prior art.

Claims 26-29 and 32-35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** (Issued July 8, 2003; Filed Sept. 8, 1999) in view of **Nagendra *et al.*** (Alcohol, 1994, vol. 11, pages 7-10), **Huang *et al.*** (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), **Ali-Osman *et al.*** (Mol. Pharm., 1996, vol. 49, pages 1012-1020), and **Hoffman *et al.*** (J. Theor. Biol., 2001, vol. 211, pages 403-407).

The instant claims are drawn to the treatment of tumors having an operative retinoblastoma protein comprising administering one or a combination from the group of disulfiram, curcumin, buthionine sulfoximine (BSO) and carmustine (BCNU).

'987 discloses that disulfiram inhibits the growth of cancer cells (Abstract; col. 2, lines 38-44). Disulfiram can also be administered in combination with another anticancer agent (col. 3, lines 10-13 and col. 7, lines 8-18). It is noted that disulfiram is an agent that causes oxidation

of GSH (see instant claim 29). '987 thus suggests administering disulfiram to treat tumors as recited in claims 26, 28, and 29.

Nagendra *et al.* disclose that chronic administration of disulfiram to rats affects GSH metabolism (Abstract). Administration of disulfiram led to a decrease in GSH with a concomitant increase in GSSG content, which would thus result in a decrease in the $[GSH]^2/[GSSG]$ ratio as instantly claimed. Brain glutathione reductase activity was also significantly depleted. The authors conclude that treatment with disulfiram decreases GSH content with a concomitant increase in GSSG level and perturbs the GSH/GSSG redox status, inducing oxidative stress on the brain. As Nagendra *et al.* is cited only for this general teaching, it follows that it is silent with respect to treating tumors.

Huang *et al.* disclose that the glutathione (GSH) level in hepatocytes increases during active proliferation (Abstract). The authors evaluated whether a similar increase is found in hepatocellular carcinoma (HCC). It is disclosed that GSH levels doubled in HCC as compared to normal liver (page 19). HepG2 liver cancer cells were grown with varying concentrations of cysteine and it was found that cell growth increased with increasing cysteine concentration (page 19, right column). Further, BSO treatment decreased GSH levels and rates of growth. Cells treated with BSO for 24 hours had significantly lower DNA synthesis than controls (page 19, right column). The authors disclose that GSH has been found to be elevated in a number of drug-resistant tumor cell lines including prostate, ovarian, lung and colorectal cancers (page 20, right column), thus suggesting that a decrease is GSH as achieved with BSO may result in a decrease in cell growth. Increased γ-L-glutamyl-L-cysteine synthetase (GCS) activity was found in the majority of these resistant tumor cells. The authors conclude that "an increase in the cellular GSH content may change the thiol-redox status of the cell that is proportional to $[GSH]^2/[GSSG]$" (page 21, right column). This change in redox state may then "affect the expression or activity of factors important for cell cycle progression". It is noted that BSO is recited as an agent that causes inhibition of the GCS enzyme (see instant claim 35). Huang *et al.* thus suggest and motivate the treatment of tumors having elevated GSH content as recited in instant claims 26, 34, and 35.

Ali-Osman *et al.* disclose that depletion of GSH by BSO (currently being explored as a means of enhancing the efficacy of cancer chemotherapy and explicitly taught in Huang *et al.*) in

human malignant glioma cells potentiated the cytotoxicity of BCNU (Abstract), thus motivating the use of BSO and BCNU together as recited in claims 26, 27, 32, and 33-35. It is noted that BCNU is an agent that causes inhibition of the glutathione reductase enzyme (see instant claim 33). Figure 1 demonstrates that GCS is significantly inhibited by BSO (page 1015). Further, exposure to BSO significantly depleted GSH (Figure 2, page 1015). Although BSO had no effect on cell survival, it did sensitize the cell lines to treatment with BCNU (Table 1, page 1017 and Figure 6, page 1018). GSH depletion is a major mechanism by which BSO enhances cellular alkylator sensitivity although there is evidence that BSO may increase drug sensitivity by other mechanisms (page 1018, right column). Ali-Osman *et al.* thus suggest and motivate the combined use of BSO and BCNU to treat tumors. The tertiary reference is silent with respect to disulfiram.

Hoffman *et al.* is cited for the general teaching that an elevated redox potential has been observed to be associated with the inability of retinoblastoma (RB) protein to be phosphorylated and with cell cycle arrest. As such, the authors suggest that an elevated redox potential can inhibit phosphorylation of RB protein, which in turn will stop cell proliferation (page 403, paragraph bridging left and right columns), thus suggesting the treatment of cancers having an operative retinoblastoma (RB) protein *via* changes in redox potential. Hoffman *et al.* further teach that application of agents that decrease GSH will increase redox potential (page 405, right column, second paragraph under the heading "Model"). For example, Hoffman *et al.* teach that addition of BSO (which is taught by Huang *et al.* to decrease GSH) to fibroblasts and fibrosarcoma cells results in a threshold potential of between -196 and -218 mV that resulted in cessation of cell proliferation (page 406, left column, first paragraph under the heading "Application of the Model to Interpreting Published Data).

In view of the above disclosures, the instant claims would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. It is well known in the art that administration of BSO depletes GSH content and enhances the cytotoxicity of BCNU. Further, disulfiram has been shown to inhibit cancer cell proliferation and decrease GSH with a concomitant increase in GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in instant claim 26). It would have been obvious to combine disulfiram, BSO and/or carmustine (BCNU) to treat tumors because from the disclosures of the '987 patent, Huang *et al.*, Ali-Osman *et al.*

and Nagendra *et al*. it is clear that disulfiram is effective at inhibiting cancer cell proliferation and that decreasing GSH cell content has a significant effect on the cytotoxicity of the chemotherapeutic drug BCNU. Thus, the skilled artisan would be imbued with at least a reasonable expectation that administering disulfiram would decrease GSH, increase GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in the instant claims), and be an effective treatment for tumors. In addition co-administration of BSO would be predicted to further decrease GSH content resulting in the sensitization of tumors to BCNU treatment.

Although ample motivation to combine the references is found in the teachings of the individual references as discussed *supra*, difulfiram and carmustine (*i.e.* BCNU) are individually known in the art as agents for treating cancers, whose efficacy when administered alone is well established for the treatment of a large number of neoplasias and metastasis. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is NOT necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption. Further, the addition of BSO to a composition of disulfiram and BCNU would have been obvious given the teachings of Ali-Osman *et al*. who disclose that BSO enhances the anticancer activity of BCNU.

Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over **U.S. Patent No. 6,589,987** in view of **Nagendra *et al.***, **Huang *et al.***, **Ali-Osman *et al.***, and **Hoffman *et al.*** as applied to claims 26-29 and 32-35 above, and further in view of **Ramachandran *et al***. (Breast Cancer Research and Treatment, 1999, vol. 54, pages 269-278).

USP 6,589,987, Nagendra *et al.*, Huang *et al.*, Ali-Osman *et al.*, and Hoffman *et al.* teach as applied to claims 26-29 and 32-35 above and are herein applied for the same teachings in their entirety. Claims 30-31 differ from USP 6,589,987, Nagendra *et al.*, Huang *et al.*, Ali-Osman *et al.*, and Hoffman *et al.* in that the cited references do not teach curcumin.

However, Ramachandran et al. teach that administration of curcumin to breast cancer cells induced apoptosis in breast cancer cells compared to a very low percentage of apoptosis in mammary epithelial cells (Abstract).

It would have been prima facie obvious to one of ordinary skill in the art to administer curcumin alone or in combination with disulfiram, BCNU, and/or BSO to treat breast cancer in a subject. The skilled artisan would have been motivated to do so because curcumin has been taught to selectively induce apoptosis of breast cancer cells versus normal breast epithelial cells and disulfiram, BCNU, and BSO have all been individually taught in the prior art to be effective antitumor agents alone and in combination with other chemotherapeutic agents. As such, it would have been obvious to one skilled in the art that curcumin combined with one or more of disulfiram, BCNU, and BSO would be effective to treat breast tumors in a subject.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614